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Chapter 8

Clinical Presentation, Diagnosis and Management of TB-HIV Comorbidity in Children

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Additional information is available at the end of the chapter

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Abstract

The problem of combination of tuberculosis and human immunodeficiency virus (HIV) infection remains urgent. Ninety percent of women with HIV infection are of childbearing age that results in increasing the number of children with HIV infection in perinatal contact. In Saint Petersburg from 2014 to 2017, about 5000 children were born from a perinatal contact for HIV infection; by 2017, more than 300 children have confirmed HIV infection. The comparative analysis of case histories of 25 children with TB/HIV combination and 50 children with tuberculosis without HIV infection was performed. Analysis of the study results showed that there are cases of late diagnosis of HIV infection. TB is detected clinically more frequently in children with HIV infection than in children without HIV infection (25 and 5%, respectively). More than one-third of the patients with coinfection had negative sensitivity to tuberculin and DST. The prevalence and the severity of TB in children with HIV infection correlates with the degree of immunosuppression. Eight percent of children had immune reconstitution inflammatory syndrome. Treatment of patients with coinfection associated in most cases with the increased period of total treatment course. Four children with HIV infection vaccinated with BCG were diagnosed with generalized tuberculosis.

Keywords: tuberculosis, HIV infection, children, diagnostics, clinic, prevention, treatment

1. Relevance of the problem of TB/HIV in children

It is generally recognized that tuberculosis is one of the main and the most common diseases associated with HIV infection. Under the WHO estimations, about 5 million people on the

planet are infected with both *Mycobacterium tuberculosis* (MBT) and human immunodeficiency virus (HIV). In 2017 in Russia at the total tuberculosis incidence of 41.6 per 100,000 of the population, the incidence of coinfection of TB/HIV was 8.4 per 100,000 or 20.2%. HIV infection facilitates the transition of the state of infection with *Mycobacterium tuberculosis* to TB disease because the immune system in people infected with HIV loses the ability to delay MBT growth and spread. The risk of TB among the HIV-infected patients is in 10–15 times higher than among HIV-negative patients [1]. In recent years there has been an increase in the number of young women with tuberculosis and HIV. Changing their reproductive behavior in favor of the maintenance of pregnancy leads to an increase in the number of children with HIV infection in perinatal contact [2]. So, across Russia in 2008, every seventh (14.6%) woman among delivered women was not followed up during pregnancy. In these HIV-positive women, the combination of HIV with tuberculosis, viral hepatitis, and other infectious diseases is possible. Social status of adults with HIV infection (drug addiction, alcoholism, low material level, etc.) increases the risk of children contact with TB-infected persons that leads to the development of the combined TB/HIV infection. In the period from 2012 to 2017 in Russia, there were about 300 cases of TB/HIV combination in children of 0–14 years old. The problem of tuberculosis and HIV coinfection is closely overlapped with the detection of *Mycobacterium tuberculosis* resistance to anti-TB medicines increasing the risk of extremely unfavorable course of tuberculosis.

2. Tuberculosis and HIV infection in children

2.1. Pathogenesis of TB/HIV coinfection

The coinfection TB and HIV may be considered as two interacting diseases. Patients with comorbidities shall be divided into the following groups: Group 1 for TB/HIV with HIV infection being the primary disease, and tuberculosis is associated with HIV (this type of coinfection prevails in children), and Group 2 for TB/HIV where tuberculosis is primary. In tuberculosis development as in HIV, the great role plays immune processes, mainly associated with lymphocytes, macrophages, and monocytes. Moreover, TB causes disturbances in the same part of the immune system that HIV infects.

2.1.1. The impact of HIV infection on TB

The level of CD4 and CD8 lymphocytes, markers of the immune system activation, and pro-inflammatory cytokines play an important role in the immune response in tuberculosis [3, 4]. The decrease in CD4 lymphocytes typical for HIV infection initiates the series of immune disorders and thus complicates tuberculosis course and prognosis. The level of IL-2 and IFN-gamma involved in the cell immunity decreases continuously. Decreased ability of mononuclear cells to migrate from the bloodstream into the lungs and changes in cytokine secretion cause the reduction of local pulmonary immunity and create conditions for active MBT reproduction, dissemination, and generalization of the tuberculous process.

2.1.2. The impact of TB on HIV infection

Tuberculosis in turn reducing the level of CD4 lymphocytes enhances HIV replication inside the cells. Mononuclear cells in the peripheral blood of patients with TB/HIV coinfection produce a greater number of tumor necrosis factor (TNF-alpha) than in patients with only TB or only HIV infection [1]. So, the development of active tuberculosis infection associated with HIV infection increases immunological disorders and promotes more rapid HIV replication resulting in impairment of the immunodeficiency and activation of reproduction of both infection pathogens. These infections result in damage and death of alveolar macrophages. While decreasing the level of CD4 lymphocytes in the zone of tuberculous inflammation, tubercles are less common and then disappear; there are no Langhans-Pirogov cells in tubercles, and epithelioid cells greatly reduce. Then, the number of macrophages may be not reduced; however, because of their defects, they are not able to form granulomas. The tissue reaction occurs mainly in the form of caseous necrosis with a large number of MBT that is associated significantly with increasing levels of tumor necrosis factor. Thus, in patients with tuberculosis and HIV infection, tubercle formation is strongly depressed or absent; alteration and exudation and caseous-necrotic changes prevail that in the future may progress and lead to a patient's death due to immune deficiency.

2.1.3. TB/HIV pathogenesis in children

Specifics of the development of TB/HIV comorbidity in children depends on infection way of children with HIV that is mainly the transmission of infection from a mother to a fetus during pregnancy and delivery. In the Russian Federation, the ratio of children infected with HIV due to perinatal transmission is 99.4% of the total number of patients with HIV infection of 0–14 years old [2]. Infection of a child from an HIV-infected mother occurs with equal frequency as in the prenatal period and during a delivery. Infection through the mother's breast milk occurs much less likely. If the virus is detected within 48 h after birth, a child is considered as infected in the prenatal period; infection during a delivery may be assumed in the case of changes of the negative results obtained in the first days of life to positive ones between 7 and 90 days of life.

Pathogenesis of HIV infection in children is determined by the peculiarities of HIV interaction with a child's body and, on the other hand, by the set of cofactors. Perinatal HIV infection affects the immature immune system of a fetus; clinical manifestation occurs earlier. Almost in 15% of children, AIDS symptoms are recorded already by the first year of life, and by 4 years old—in 50% of children. In newborns immunosuppression with significant decrease of CD4 cells comes quickly. In young children earlier there is a failure not only of T-cell but also B-cell immunity system. The decrease in the antibody productions determines a high frequency of bacterial infection recurrence [1].

Due to perinatal HIV infection of children, TB/HIV coinfection had some features in comparison with adults: (1) the risk of TB/HIV coinfection from an early age; (2) HIV infection is always primary in relation to tuberculosis (in adults it may be vice versa); (3) more rapid

progression of HIV infection associated with perinatal infection; (4) development of severe generalized forms of tuberculosis due to the age failure of the immune system increased by the development of HIV infection; and (5) MBT infection often occurs as a result of family contact with active TB patients.

2.2. Specific aspects in detection and diagnosis of tuberculosis in children with HIV infection

Tuberculosis is the specific infectious disease without pathognomonic symptoms in any location; in this regard, tuberculosis diagnostics remain quite complex and require the comprehensive evaluation of all the results obtained. HIV infection complicates the assessment of the obtained data, because the interpretation of immunological parameters and tuberculin tests may not always be correct in these cases.

The main methods of early detection of TB in children with or without HIV infection are immunodiagnostics, the epidemiological method, the method of work with risk groups, and the clinical method [4].

2.2.1. Immunodiagnostics

Immunodiagnostics means performing specific diagnostic tests using antigens of *Mycobacterium tuberculosis* to identify sensitization (infection) of the organism with *Mycobacterium tuberculosis* that cause, under certain conditions, the development of tuberculosis. Diagnostic tests include the conventional Mantoux test, the test with the tuberculous recombinant allergen and immunological and cell tests in vitro.

2.2.1.1. Conventional tuberculinodiagnosis

Mantoux intracutaneous test with 2 TU of PPD-L. The medicine—tuberculosis allergen—is purified in standard dilution with 2 TU per 0.1 mL. When intracutaneous introduction of tuberculin causes specific skin allergic reaction of delayed hypersensitivity in the case of MBT infection or in the first years after BCG vaccination, the severity of the reaction may be negative, doubtful (a wheal of 2–4 mm, hyperemia of any size), positive (5 mm or more), and hyperergic (17 mm and more).

2.2.1.2. Diaskin test

Diaskin test (the recombinant tuberculosis allergen) is the test for tuberculosis immunodiagnostics developed by Russian scientists on the basis of features of the virulent *Mycobacterium tuberculosis* genome of the BCG vaccine strain [5]. It is the recombinant protein produced by genetically modified *Escherichia coli* containing two specific antigens ESAT-6 and CFP-10 that are present in virulent, actively reproducing *M. tuberculosis* and *M. bovis* but are absent in *M. bovis* BCG and saprophytic mycobacteria. One dose (0.1 mL) of the product contains recombinant protein in the amount of 0.2 μg. When intracutaneous introduction of the

tuberculosis recombinant allergen causes the specific skin reaction of delayed hypersensitivity in most persons with active tuberculosis infection in patients vaccinated with BCG and non-infected with MBT, there is no reaction to this test. Diaskin test response may be negative, doubtful (only hyperemia), positive (a wheal up to 14 mm), and hyperergic (a wheal more than 15 mm).

2.2.1.3. Immunologic cell tests in vitro

These tests are based on releasing interferon-gamma (IFN-gamma) by T lymphocytes. The QuantiFERON-TB Gold test stimulates the T lymphocytes of a patient's blood with recombinant proteins ESAT-6 and CFP-10 that in the presence of specific sensitization of T lymphocytes produce interferon-gamma measured by the enzyme-linked immunosorbent assay (ELISA) [6].

The T-SPOT.TB test using the ELISpot method determines the number of mononuclear cells of the peripheral blood that produce IFN-gamma in response to stimulation by antigens ESAT-6 and CFP-10.

Detection of immune response to the antigens ESAT-6 and CFP-10 indicates the presence of tuberculosis infection in the body. Thus, the tests QuantiFERON-TB Gold and T-SPOT.TB give positive results both in latent tuberculosis infection and active tuberculosis. Patients with TB/HIV skin tests with tuberculosis allergens and immunological in vitro tests have often false-negative results due to the immunity lack.

2.2.2. The epidemiological method

The epidemiological method is based on the number of events among persons in contact with tuberculosis patients and is aimed at early identification of the disease in these children. Prolonged contact with TB patients is dangerous for a child of any age. The risk of developing the disease of parents is particularly enhanced by drug addiction, alcoholism, a stay in a prison, and poor material living conditions that in turn increases the risk of a child's disease in a family of a patient with tuberculosis. The above-specified confounding factors not only increase the risk of developing tuberculosis but also make the measures for TB detection difficult.

Children with HIV infection in contact with TB patients are at an increased risk, because human immunodeficiency virus negatively impacts the immune-competent cells responsible for TB immunity. In this regard, all contacting children are registered in TB dispensaries. The frequency of control examinations of children from centers of high epidemiological risk is one time every 3–4 months, from less dangerous areas—one time per 6 months.

2.2.3. Work with risk groups

TB risk groups include children with newly positive hyperergic sensitivity to tuberculin, increase of tuberculin reactions, and no BCG vaccination, children with chronic diseases of different organs and systems, and children with HIV infection. These children have

immunodiagnostics two times a year. At the same time, children infected with MBT with undetermined HIV infection but with a history of frequent recurrent pneumonia and bronchitis, with confirmed cytomegalovirus, herpes infection, hepatitis B and C, lymphoid interstitial pneumonia, cardiomyopathy, recurrent bacterial infections, and long-lasting low-grade fever, shall be tested not only for tuberculosis but also for HIV.

2.2.4. Clinical method

In some children TB develops with severe clinical symptoms. The symptoms may be similar to other diseases—tuberculosis "masking." The change in a child's condition is not improved for a long period but is persistent and forced to go to the hospital. Clinical, laboratory, and radiological data suggest a local form of tuberculosis. This method of detection is the most relevant in the group of children of early age, when often there are mild reactions to tuberculin, not allowing to suspect tuberculosis; also, some children with HIV infection may not always indicate the presence or absence of MBT infection due to sensitivity to tuberculin in this category of patients.

We analyzed the medical records of 75 children with TB and hospitalized in the TB department of Children Infectious Hospital No. 3 of Saint Petersburg since 2010 till 2017. The age of children is from 1 to 14 years old. Patients were divided into two groups:

Group 1 is the main group with 25 children with TB and HIV combination (TB/HIV).

Group 2 is the comparison group with 50 children with tuberculosis without HIV infection (TB).

All children in the hospital underwent complex clinical and laboratory examination using intracutaneous tests with tuberculosis allergens, X-ray examination, and MSCT, the bacteriological study.

According to our research data, in the group of children with tuberculosis and HIV infection, local forms of tuberculosis were detected with the change of the sensitivity to tuberculin in 44% of cases (11 patients); in the group of patients without HIV infection, tuberculosis was detected by the method of tuberculinodiagnosis in 56% of cases (28 children) ($p = 0.1$). The disease was detected during examination associated with the contact in the group of children with TB/HIV coinfection in 28% (7 children), while in the children without HIV in 40% of cases (20 children) ($p = 0.1$). However, in patients with HIV infection, tuberculosis was detected more frequently than in children without HIV when visiting a doctor with clinical complaints. So, in Group 1 TB was detected by the clinical method in 28% of cases (7 children), whereas in Group 2, in 4% of cases (2 children) ($p = 0.04$).

During the study, we also analyzed the terms of HIV infection detection in patients. Thus, of the 25 children with TB/HIV, 24 ones had confirmed perinatal HIV infection contact; for 1 child HIV infection of the mother was not determined. HIV infection in 11 children (44%) was confirmed in the first months of life, and later in 14 children (56%) among them in the first 3 years, in 9 patients, at the age of 6–13 years old, in 5 children. It should be noted that in four children (7, 8, 9, and 13 years old), HIV infection was detected under the diagnostic examination for tuberculosis. HIV infection diagnostics in children in the later periods may

be associated with a long seronegative period in the development of HIV infection and insufficient control of examination of pregnant women from risk groups.

2.2.5. Tuberculosis diagnostics in children with HIV infection

Diagnostics is carried out only in specialized tuberculosis facilities. When suspecting TB in children with HIV infection, the complex of diagnostic measures is applied, including the thorough history, the physical examination, and laboratory tests of blood and urine; the chest plane X-ray examination, the chest and the abdomen MSCT, bronchoscopy, and abdominal ultrasound examination; sputum, urine, epithelial lining fluid MBT test (microscopy, solid medium inoculation, BACTEC, PCR), and immunodiagnostics.

2.2.6. History

Collecting the anamnesis, a physician shall identify factors that could contribute to the development of both HIV infection and tuberculosis. The great attention shall be paid to a perinatal history: diseases of the mother prior and during pregnancy, especially the presence of a hepatitis B and C, HIV, drug addiction, alcoholism, gestation course, parents' lifestyle, and social status. The above factors place a child at the high risk of infection not only with HIV and hepatitis B and C but also with MBT. The analysis of the socio-epidemiological factors in groups of our patients demonstrated that the deprived social background was observed in 100% patients of Group 1 and in 60% of children of Group 2 ($p < 0.01$). Family and relative contacts with tuberculosis patients were more often detected in children with TB without HIV infection in 71% of cases, whereas in the group of children with TB/HIV, in 50% of patients. HIV infection is detected in mothers of children of Group 2 in 18% of cases and in patients of Group 1, in 96% of cases ($p = 0.01$) (for one child HIV infection of the mother was not determined). Parents' drug addiction and alcoholism were detected in the majority in the group of children with tuberculosis and HIV infection (85%), while in the group of children without HIV infection, in 22% of cases ($p = 0.02$).

It should be find a child's endured diseases and concomitant pathology, the presence of cytomegalovirus, herpes infections, the frequency of respiratory infections, the presence of chronic diseases, allergic reactions, etc.

A phthisiatrician shall always obtain information about vaccination, especially BCG vaccination and revaccination, and the history of Mantoux tests. Due to the absence of BCG vaccination in children with HIV, the presence of suspicious or positive reaction to tuberculin is the indication for the enhanced examination as such a result may not be indicative of postvaccination allergy.

2.2.7. Physical examination

In children with TB/HIV coinfection, there is more evident asthenization; in some cases, there may be failure to physical development.

Children usually have pale grayish skin and "shadows" under the eyes. There is no postvaccinal scar on the skin of the shoulder in children with HIV infection due to medical exemption

from BCG vaccination. Children with TB/HIV have dry skin, decreasing the subcutaneous fat tissue, long-term course of the disease, and the decrease in tissue tension. There are palpable peripheral lymph nodes more than six to seven groups (cervical group, supra- and sub-clavicular, axillary, thoracic, cubital, inguinal ones) enlarged up to 1 cm or more. Under palpation of the abdomen, the liver and the spleen are moderately enlarged. In rare cases, there are enlarged mesenteric lymph nodes.

Percussion and auscultation changes depend on the form of tuberculosis, the lesion volume, the extent of the process, the presence of complications, and a child's age. At the various local forms, it is possible to determine the zone of percussion sound shortening in the lung tissue, regions of hyperresonant resonance. There are no commonly distinct symptoms with limited forms by auscultation. With more severe lesions of the lung tissue, the type of breathing may change, and rattling appears. More often, these symptoms appear in children of early age with the complicated course, particularly in bronchopulmonary lesions.

2.2.8. Radiology diagnostics

Sectional roentgenography remains the leading method in the diagnostics of tuberculosis in children with and without HIV infection. X-ray diagnostics uses digital or analogue chest X-ray, linear tomography, multislice computed tomography, and ultrasound. During the initial examination of a child, the attention shall be paid to the presence of lesions and foci in the pulmonary tissue, dimensions, and structuredness of the lung roots. In recent years, the method for multislice computed tomography has the greatest diagnostic value. This method is more informative and more clearly demonstrates the location, the extent of the process, the structure of the lymph nodes, the presence of small foci, and the calcifications in areas that are poorly visualized under standard X-ray examinations. Chest ultrasound examination is used when suspecting the presence of liquid in the pleural cavity, for the differential diagnosis of fibrosing aortic ligament and calcifications of the intrathoracic nodes in this area.

2.2.9. Bronchoscopy

This study helps to assess the condition of the bronchial tree in children, to identify specific lesions of the bronchi, the presence of indirect signs of the intrathoracic lymph node enlargement. During bronchoscopy the material is sampled for bacteriological, immunological, and cytological tests. In the cases of tuberculosis and HIV coinfection, this method has an important diagnostic value.

2.2.10. Abdominal ultrasound examination

In children with TB with or without HIV infection, enlargement of the liver and the spleen, changes in the organ tissue structure, the presence of the lymph nodes at the gate of the liver and the spleen, hyperechogenic inclusions in the spleen, calcifications, abnormal changes in the kidneys, and enlarged mesenteric lymph nodes are found.

2.2.11. Immunodiagnostics

The analysis of tuberculin test and DST results in our patients demonstrated the following findings. Under the Mantoux test with 2 TU, the positive results are detected in the group

of patients with TB/HIV in 10 children (40%), and in the group of patients with TB without HIV infection, in 34 children (68%) (p = 0.05). Hyperergic reactions were in 5 children with TB/HIV (20%) and in 16 children with TB and with or without HIV infection (32%). Negative sensitivity was detected only in patients of Group 2, 10 cases (40%) (p = 0.03), that correspond to the literature data [7]. According to the results of DST, the positive results were more often detected in children without HIV infection in 34 children (68%), and in patients with TB/HIV, the positive sensitivity to Diaskin test was observed in eight children (32%) (p = 0.04). Hyperergic reactions was observed in 8 children of Group 2 (16%) and 3 children of Group 1 (12%) (p = 0.09), while the negative results were detected with greater frequency in the group of children with TB/HIV, in 14 children (56%), than in the group of children with TB without HIV infection—in 8 children (16%) (p = 0.04).

2.2.12. Laboratory diagnostics

The severity of hemogram changes depends on the form, the phase, and the presence of process complications. Children with tuberculosis and HIV infection have long-lasting anemia, thrombocytopenia, and a more evident and persistent increase of ESR. A smaller part of children with TB with or without HIV infection may have moderate proteinuria and erythrocyturia. Biochemical blood count in children with TB and HIV shows a sharper increase of beta-lipoproteins and gamma globulins, reducing the overall level of albumins. Such values of biochemical parameters may indicate the activity of tuberculous process and the immune system disorder in a child with HIV.

The complex examination of children with suspected tuberculosis (without HIV) mandatorily includes the blood test for HIV; hepatitis A, B, and C; and under indications—for cytomegalovirus, herpes virus, etc. If HIV is found, a child shall be examined and then constantly followed up in an infectious disease center.

2.2.13. Bacteriological study

To verify the TB diagnosis, the following shall be studied: sputum, pleural liquid, urine, cerebrospinal fluid, the lymph nodes, punctates, etc. For children the gastric lavage study is optimal. Smear microscopy and culture study (solid and liquid medium inoculation) are performed. Molecular and genetic study methods are used. The most widely used method is the polymerase chain reaction with the specific MBT primer. Among our patients with TB/HIV coinfection in only one case, MBT was extracted by solid medium inoculation; in other children the results of bacteriological studies were negative. So, in connection with the difficulties of diagnostics of tuberculosis in children with HIV infection, one cannot rely on the clinical minimum used for tuberculosis in children without comorbidities. For children with HIV infection, all obtained results shall be comprehensively evaluated.

2.3. Clinical forms and progression of tuberculosis in children with HIV infection

Clinical signs of tuberculosis in all age groups depend on the stage of HIV infection. The structure of clinical forms, clinical signs, frequency of bacterial excretion, and the effectiveness of treatment in patients with indicators of CD4 close to the norm do not differ from those in the group of HIV-negative patients. At lower CD4 tuberculous inflammation gradually

loses classic features and is characterized by an atypical course. In the structure of clinical forms, the disseminated forms begin to prevail creating extrapulmonary lesions in the lymph nodes, the intestines, the liver, the spleen, and the meninges.

HIV infection depending on the stage and the condition of the cell immunity may also impact on the clinical signs of tuberculosis in children. A child's age, the duration of contact with TB patients, the lesion form and area, and the presence of complications affect the course and symptoms of tuberculosis.

In the structure of clinical forms of our patients both in the group of children with tuberculosis and HIV infection and in the group of children with tuberculosis without HIV infection, tuberculosis of the intrathoracic lymph nodes prevails—in 56 and 78%, respectively ($p = 0.8$). At the same time, in the group of children with TB/HIV coinfection, primary tuberculosis complex was detected with greater frequency in six cases (24%) and generalized tuberculosis in 20% of cases (five children), whereas in the group of children without HIV, primary complex was diagnosed in six children (13%) and generalized forms in two children (4.1%) ($p = 0.05$). Our studies demonstrated the dependence of the TB form on the severity of immunodeficiency and viral load. So, severe generalized forms of tuberculosis were diagnosed in children with severe immunodeficiency—CD4 from 2 to 9% and high viral load from 675,000 to 1 million cop/mL. At low viral load, from 65,000 to 480,000 cop/mL, and moderate immunosuppression, CD4 from 15 to 34%, children had tuberculosis of the intrathoracic lymphatic nodes or primary tuberculous complex in the phase of infiltration, induration, or calcification.

2.3.1. Tuberculosis of the intrathoracic lymph nodes and primary tuberculosis complex in children with HIV infection

In clinical signs of primary forms of tuberculosis in children with HIV infection, in most cases evident intoxication syndrome prevails; in the majority there are evident such as emotional lability, mood swings, depression, and sometimes negativity and unmotivated aggression toward others.

The intoxication syndrome appears in the form of decreased body weight, periorbital cyanosis, the evident pale grayish skin, and reduced tissue tension. Under studying clinical symptoms and laboratory indicators, we found that the decrease in the body weight was observed in the group of children with TB/HIV coinfection in 52% of children. Low-grade fever was detected in the majority (85%) of patients with HIV infection. Hepatosplenomegaly by palpation and under abdominal ultrasound examination and enlargement of the liver and the spleen in 1 cm and more against normal age-related indicators are found. So, the enlarged liver and spleen were observed in 68% of patients. The constant symptom accompanying the primary forms of tuberculosis and HIV infection in 100% of cases is peripheral polyadenopathy. In such children the palpable multiple peripheral lymph nodes (more than six in groups) with polymorphism are seen: from small and dense to large ones with periadenitis; enlarged cervical, supra- and sub-clavicular, thoracic, cubital, and inguinal groups of the lymph nodes are also seen. Typically, in primary forms of tuberculosis, percussion symptoms prevail in the chest. In primary tuberculous complex, especially with significant lung affect (that is observed in children of early age), there is shortening of the percussion sound over the affected area. In

primary tuberculous complex, hard breathing and also weakened breathing over the lesion may be detected by auscultation; sometimes, there is rattling. A hemogram of children with primary forms of tuberculosis and HIV infection shows hypo- or normochromic anemia (according to our data in 40% of children), moderate leukocytosis, and lymphopenia at the early stages with subsequent lymphocytosis. These children have significant ESR increase: from 20 to 60 mm/h. Most children with the comorbidity had recorded PLT decrease associated with HIV infection. The above changes of blood parameters retained in children with TB/HIV for more periods of term with slower normalization even against the combined therapy (for up to 6 months). Under biochemical parameter study (according to our studies) in children with TB and the initial signs of HIV infection, there is less increase of gamma globulin fractions; more often in these children, there is a decrease of concentrations of gamma globulins and increased alpha-2 globulins. At the same time, children at the later HIV stages (severe immunodeficiency) have the sharp increase of gamma globulins (up to 30–42%). Under X-ray exam in the presence of the enlarged intrathoracic lymph nodes, the mediastinum shadow is expanded with changes in the shadow outlines. Due to periadenitis the nodes are merged into packages with polycyclic boundaries. Some children had calcium inclusions in the thoracic lymph nodes (20% of cases). In primary tuberculosis complex, radiologically, there is a focus of different sizes located mainly in the upper regions, less in the lower segments. There is the lymph path from the primary affect to the enlarged regional lymph nodes of the root. In children of early age, the pulmonary component usually is located in the root zone, often in the lower sections. When detecting the disease at the later stages, calcium inclusions may be visualized in the area of primary affect and in the lung root.

2.3.2. Tuberculosis complications

The course of the tuberculosis process in studied children with HIV is characterized by a tendency to a prolonged course, slow regression, complications of the process (bronchopulmonary lesions, seeding in the lung tissue when affecting the intrathoracic lymph nodes), and frequent outcomes with the calcification formation. Complicated course of tuberculosis in children with HIV infection according to our observations was diagnosed in ten children (40.2%), five of them (20%) have the generalized form of tuberculosis. Complicated course presents the development of atelectasis in one child, bronchopulmonary lesion in two children, and seeding in the lung tissue in two children. Tuberculous process relapse was observed in two children, and recurrence in 2 years after the end of TB treatment was developed in one child of a younger age. The reasons for the complicated course are the late detection of tuberculosis in children with HIV infection, late onset of therapy, and the negative impact of HIV on the course of tuberculosis. TB acute condition or relapse was caused in all cases by cessation of antiretroviral therapy (due to the negative attitude toward the treatment of the parents) that resulted in a decrease of the immunity and, as a consequence, the relapse of the tuberculous process.

2.3.3. Generalized tuberculosis in children with HIV

The development of such severe form in children with HIV infection may be associated with the late detection of tuberculosis due to negative sensitivity to tuberculin under the planned tuberculinodiagnosis in HIV-infected children; according to some authors, the lack of BCG

vaccination at birth and vaccination later than in 18 months; long closed contact with TB patients against adverse social conditions [4].

The disease begins acutely in children of early age and in older children begins gradually with condition worsening to severe. The temperature rises to 39–40°C, intoxication symptoms and weakness are strongly evident. Some children have short breathing, cyanosis, and dry cough. Children with TB/HIV may have symptoms of herpes infection and candidiasis. At the same time, the absence of evident objective changes against the general severe condition of a child is conspicuous. There are multiple palpable lymph nodes in seven to nine groups; the liver and spleen are enlarged significantly. There is hyperresonant sound resonance over all lung fields by percussion, decreased breath by auscultation, and mild moist rale auscultated better in the paravertebral areas.

In the blood of children with HIV infection, there is more evident increase of ESR (up to 60 mm/h), anemia, and thrombocytopenia. Tuberculin sensitivity in the cases of generalized tuberculosis in children with HIV infection almost in all cases is negative. In the absence of typical clinical and laboratory findings inherent to the generalized forms of tuberculosis, the X-ray method remains determinant. In the early period (the first week of the disease), there is weakening of the lung pattern and unusual ripple; in 7–10 days, there is evident dissemination of clear uniform lesions in the lung tissue in the form of event rashes with a diameter of 2–3 mm. At the same time, as a rule, in children enlarged intrathoracic lymph nodes are found, because they are the source of dissemination; the cases of disseminated processes with the lung tissue degradation are described. When detecting dissemination, the study of other organs and systems shall be performed (ophthalmologist examination, abdominal ultrasound, and CT studies). In all our patients with generalized tuberculosis (five children) along with affection of the lungs and the intrathoracic lymph nodes, the affected peripheral lymph nodes, the mesenteric lymph nodes, and the spleen nodes were seen; two children had tuberculous meningoencephalitis.

Bacteriological study usually does not show positive results. Diagnostically significant method in these cases may be the molecular genetic diagnostics (PCR).

2.3.4. Comorbidity

We analyzed the frequency and the nature of comorbidity in patients with TB/HIV. So, chronic recurrent herpes infection in children with tuberculosis and HIV infection was diagnosed in 17 patients (68%). Signs of allergic dermatitis were observed in 10 (40%) children with TB/HIV; candidiasis was diagnosed in five patients (20%). In the group of children with TB/HIV, there is one case of thrombocytopenic purpura (4%). Viral hepatitis B was observed in two children with TB/HIV (8%), viral hepatitis C in three patients in this group (12%), and toxoplasmosis and cytomegalovirus infection in one child (4%).

2.4. Difficulties in the treatment of tuberculosis in children with HIV infection

In the treatment of tuberculosis in children with or without HIV infection, the main principles of therapy shall be met [8]. For children with HIV infection, the important point is the joint

follow-up of such patient by a phtisiologist and an infectiologist, because a patient receives simultaneously two kinds of therapy. The antituberculous and antiretroviral medicines have mutual con-founding toxic effects moreover, in children, HIV may be associated with secondary diseases (cytomegalovirus, herpes infection, etc.). TB chemotherapy includes two phases—the intensive phase (the maximum number of TB drugs to achieve significant effect) and the continuation phase. The treatment is performed in accordance with therapy regimens using TB medicines of the primary and alternative series. Indications for initiation of antiretroviral therapy in patients with comorbidity do not differ from the indications for treatment of patients with HIV infection without tuberculosis. Currently, there is no conclusive evidence that prolongation of TB therapy for over 6 months in patients with HIV infection improves treatment results. At the same time, the prolonged treatment (up to 8–9 months) is still more preferable in these patients due to reducing relapses compared with short-term chemotherapy. When detecting drug-resistant tuberculosis or at the high risk of tuberculosis with multidrug resistance of the pathogen (TB), children with HIV infection receive alternative medicines under life-saving indications. Antiretroviral therapy (ARVT) shall be indicated for children with tuberculosis regardless of the level of immunosuppression in 2 weeks after starting TB treatment to prevent the development of immune reconstitution inflammatory syndrome. Immune reconstitution inflammatory syndrome occurred in two children (8%) with HIV infection detected at once with tuberculosis, with severe immunodeficiency. Immune reconstitution inflammatory syndrome appeared in the form of impairment of the clinical condition of children and the progression of dissemination in the lung tissue in one case and increase of infiltrative changes and size of the intrathoracic lymph nodes in the second case. Most patients in both groups received therapy under regimen I, but children of Group 1 in most cases required an individual approach due to ARVT and the presence of comorbidities. According to our research data, the intensive phase of treatment with four TB drugs for children with TB/HIV was performed in 31% of cases, and the remaining 69% received three chemotherapy medicines. The duration of the intensive phase of chemotherapy in 43% of children with TB/HIV was more than 6 months, only in one-third of cases up to 3 months, the rest 3–6 months. The total duration of treatment was 9–12 months only in 50% of the patients; in one-third of cases, the therapy lasted 18–24 months. Cancel of antituberculosis drugs was required by 26% of children in this group due to intolerance symptoms. We established the relationship between the level of immunosuppression and the duration of the intensive phase of chemotherapy. All children with the severe immunosuppression received the treatment in the intensive phase for 6–9 months that exceeds the recommended duration of the therapy. A longer treatment of children with tuberculosis and HIV infection coinfection is caused by the evident toxic effect both of TB and antiretroviral medicines, also due to the addition of secondary disorders and intercurrent diseases required by the treatment.

2.5. Features of tuberculosis prevention in children with HIV infection

2.5.1. BCG vaccination

Now, tuberculosis immunization is one of the main and most effective methods of tuberculosis prevention among children. BCG vaccination of children born by HIV-infected mothers is ambiguous, since the administration of live vaccines against the immunodeficiency may

not only cause severe postvaccination complications but the progression of HIV infection. In Russia until 2010, BCG vaccination was allowed after the complete exclusion of HIV infection in a child of 18 months of age [9].

Currently, due to the implementation of prevention of HIV transmission from a mother during gestation and delivery, the frequency of children infection was reduced from 40 to 2%. Considering this fact, the prohibition to administer the BCG vaccine to children born from HIV-infected mothers was lifted in the absence of a child's immunodeficiency and after a three-stage prevention of HIV infection.

According to our data, among 25 children with subsequent TB/HIV, 17 children (68%) were vaccinated with BCG vaccine. However, 10 children of 17 vaccinated ones (58.8%) were immunized in a maternity hospital, the remaining eight children—at a later time—in 6 months to 2 years old. Subsequently, generalized forms of tuberculosis were diagnosed in four children vaccinated earlier with BCG; two of them had suspected generalized BCG infection. Thus, in the presence of immunodeficiency, immunization with the BCG vaccine increases the risk of a transient increase of HIV replication and the development of postvaccination complications with the generalization of BCG infection.

2.5.2. Preventive treatment and chemoprophylaxis of tuberculosis

When prescribing the preventive treatment and the chemoprophylaxis, the additional TB risk factors shall be considered:

the lack of BCG vaccination (BCG-M), in contact with a TB patient, the age of children between 3 years old and adolescence, and chronic nonspecific diseases of different organs and systems, immunodeficiency, drug abuse, low material level, migration, and homelessness among children and adolescents.

Children and adolescents for the preventive treatment shall be selected by a phtisiologist, if necessary together with a specialist in HIV infection.

Preventive treatment is performed for children: due to contact with a tuberculosis patient, with latent tuberculosis infection (in the case of positive results of DST and tests with tuberculous antigens in vitro), hyperergic reaction to tuberculin, the enhancing reaction to tuberculin, MBT in combination with nonspecific risk factors, and in the presence of the immunodeficiency.

The preventive treatment of tuberculosis for children with HIV infection is carried out depending on the level of the immunodeficiency. In the absence of immunodeficiency at the early stages of HIV infection, the preventive treatment is carried out under the general rules. The duration of the preventive treatment with doubtful and positive reaction to Diaskin test is not less than 6 months with two TB medicines. In the presence of immunodeficiency, the chemoprophylaxis shall be prescribed individually. With a moderate immunodeficiency and negative results of immunodiagnostics, the preventive treatment is prescribed for 3–6 months with two TB medicines. For significant and severe immunodeficiency, the preventive treatment is indicated regardless of the results of immunodiagnostics with two TB medicines to increase CD4 over the criteria of the evident immunodeficiency, but not less than 6 months.

The basic medicines for the preventive treatment are isoniazid and pyrazinamide (ethambutol, less rifampicin are used).

According to our data, among all patients with TB/HIV, the preventive treatment was prescribed only to four children (16%). In this case, only one child received the complete treatment; the others received incomplete courses. Incomplete coverage of these patients with the preventive treatment may be associated with tuberculosis detection prior to diagnosis of HIV infection in some children, with antisocial behavior of parents and non-compliance of the recommendations and refusal from the preventive treatment.

3. Conclusion

Thus, tuberculosis and HIV infection in children are the serious problems of the modern medicine. There is the tendency to increasing the number of children with tuberculosis and HIV infection due to the increase in the number of patients with HIV and tuberculosis among young women, in most cases, with antisocial lifestyle. The presence of immunodeficiency of varying severity in children with HIV infection makes early detection and diagnosis of tuberculosis by conventional methods difficult and requires the use of a wide range of diagnostic procedures and the use of new diagnostic methods.

The treatment of children with TB/HIV coinfection due to the late TB detection also has certain features. These children shall be followed up jointly by a phtisiologist, an infectiologist, and a pediatrician. BCG vaccination, chemoprophylaxis, and preventive treatment of these children require a differentiated approach in each case. Promotion of the healthy lifestyle, the fight against drug addiction, and improving health literacy, especially among young persons and women of reproductive age, are important for the prevention of the development of tuberculosis and HIV in children.

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